Amendments to the Specification:

The paragraph numbering for the amendments to the specification correspond to paragraph numbering in the clean copy of the substitute specification filed by amendment on June 21, 2004.

Please delete paragraph [0025].

Please delete paragraph [0026].

Please amend paragraph [0058] as follows:

Polynucleotides encoding human ß-secretase were obtained by PCR cloning and hybridization techniques as detailed in Examples 1-3 and described below. ~~FIG. 1A shows the sequence of a polynucleotide (SEQ ID NO: 1) which encodes human ß-secretase. Polynucleotides encoding human ß-secretase are conveniently isolated from any of a number of human tissues, preferably tissues of neuronal origin, including but not limited to neuronal cell lines such as the commercially available human neuroblastoma cell line IMR-32 available from the American Type Culture Collection (Manassas, VA; ATTC CCL 127) and human fetal brain, such as a human fetal brain cDNA library available from OriGene Technologies, Inc. (Rockville, MD).~~

Please delete paragraph [0059, [0060], and [0061].

Please delete paragraph [0069].

Please delete paragraphs [0075], [0076], [0077], [0078], [0079], and [0080].

Please delete paragraph [0084].

Please amend paragraph [0085] as follows:

The full-length open reading frame (ORF) of human ß-secretase is described above, and its sequence is shown in FIG. 2A as SEQ ID NO: 2. However, as mentioned above, a further

discovery of the present invention indicates that the active, naturally occurring molecule is truncated at the N-terminus by about 45 amino acids. That is, the purified protein was N-terminal sequenced according to methods known in the art (Argo Bioanalytica, Morris Plains, NJ). The N-terminus yielded the following sequence: ETDEEPEEPGRRGSFVEMVDNLRG... (SEQ ID NO: 55). This corresponds to amino acids 46-66 of the ORF-derived putative sequence. ~~Based on this observation and others described below, it is believed that the N-terminus of the active, naturally occurring, predominant human brain form of the enzyme is amino acid 46, with respect to the full-length β-secretase molecule.~~ Further processing of the purified protein provided the sequence of an internal peptide: ISFAVSACHVHDEFR (SEQ ID NO: 56), which is amino terminal to the putative transmembrane domain, as defined by the ORF. These peptides were used to validate and provide reading frame information for the isolated clones described elsewhere in this application.

Please delete paragraph [0086].

Please amend Table 3 in paragraph [0087] as follows:

Source	Est. Amount (pmoles)	~~N-terminus~~	Sequence
Human brain	1-2	~~46~~	ETDEEPEEPGR... (SEQ ID NO:3)
Recombinant, 293T	~35	~~46~~	ETDEEPEEPGR... (SEQ ID NO:3)
	~7	~~22~~	TQHGIRL(P)LR... (SEQ ID NO:4)
	~5	~~63~~	MVDNLRGKS... (SEQ ID NO:5)
Recombinant, CosA2	~4	~~46~~	ETDEEPEEPGR... (SEQ ID NO:3)
	~3	~~58~~	GSFVEMVDNL... (SEQ ID NO:6)

Please delete paragraphs [0088] and [0089].

Please delete paragraphs [0092], [0093], [0094], and [0095].

Please amend paragraph [0097] as follows:

Following expression and purification, the protein is adjusted to a concentration of about 1-20 mg/ml. In accordance with methods that have worked for other crystallized proteins, the buffer and salt concentrations present in the initial protein solution are reduced to as low a level as possible. This can be accomplished by dialyzing the sample against the starting buffer, using microdialysis techniques known in the art. ~~Buffers and crystallization conditions will vary from protein to protein, and possibly from fragment to fragment of the active ß secretase molecule, but can be determined empirically using, for example, matrix methods for determining optimal crystallization conditions. (Drentz, J., *supra;* Ducruix, A., *et al.,* eds. *Crystallization of Nucleic Acids and Proteins: A Practical Approach,* Oxford University Press, New York, 1992.)~~

Please delete paragraph [0114], including Table 5, and paragraphs [0115], [0116], [0117], and [0118].

Please delete paragraph [0125].

Please amend paragraph [0140] as follows:

A host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the protein include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be important for correct insertion, folding and/or function. ~~For example, in the case of ß secretase, it is likely that the N terminus of SEQ ID NO: 2 is truncated, possibly at amino acid 46, or at about residues 57 58 of SEQ ID NO: 2.~~ Different host cells such as CHO, HeLa, BHK, MDCK, 293, WI38, etc. have specific cellular machinery and characteristic mechanisms for such post-translational activities and may be chosen to ensure the correct modification and processing of the introduced, foreign protein.

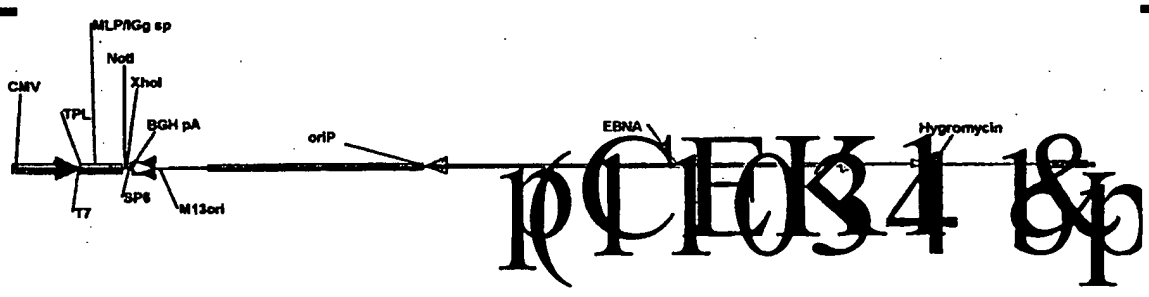
Please amend paragraph [0146] as follows:

The present invention also includes methods for identifying molecules, such as synthetic drugs, antibodies, peptides, or other molecules, which have an inhibitory effect on the activity of ß-secretase described herein, generally referred to as inhibitors, antagonists or blockers of the enzyme. Such an assay includes the steps of providing a human ß-secretase~~, such as the ß-secretase peptide~~, contacting the ß-secretase with a test compound to determine whether it has a modulating effect on the activity of the enzyme, as discussed below, and selecting from test compounds capable of modulating ß-secretase activity. In particular, inhibitory compounds (antagonists) are useful in the treatment of disease conditions associated with amyloid deposition, particularly Alzheimer's disease.

Please delete paragraphs [0177] and [0178].

Please amend paragraph [0191] as follows:

[0191] A human primary neuronal cell library in the mammalian expression vector pCEK2 vector was generated using size selected cDNA, and pools of clones generated from different sized inserts. The cDNA library for ß-secretase screening was made with poly(A)$^+$ RNA isolated from primary human neuronal cells. The cloning vector was pCEK2 (map shown below).

[[[

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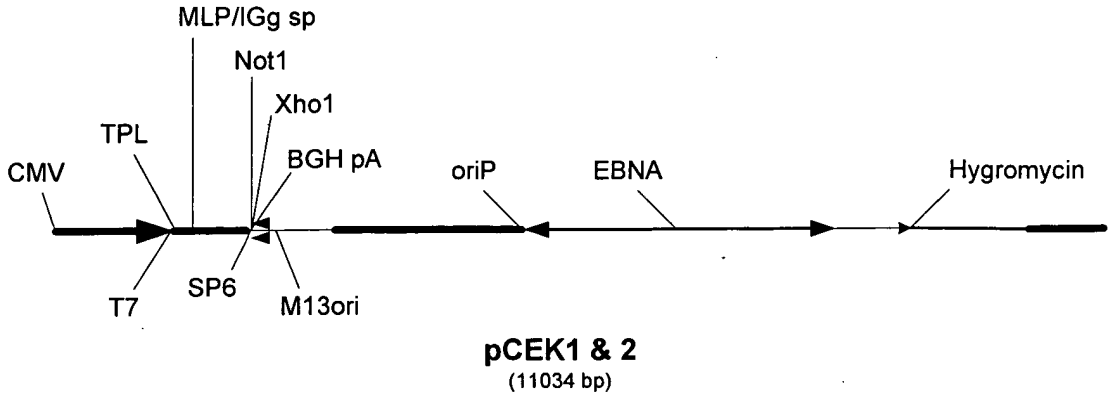

Please delete paragraph [0228].